REMARKS

The present invention relates to the assay of free and complexed troponin isoforms in patient samples. Specifically, the invention describes assay methods and kits that comprise antibodies specific for various cardiac troponin forms. Assays may use an antibody or antibody cocktail that binds to one or more specific troponin form, or that binds all forms. The assay methods and kits of the present invention can be used to diagnose unstable angina and/or myocardial infarction.

Claims 85-96, 102-106, and 114-142 are presently pending in the instant application. The Examiner indicated in Paper No. 25 that claims 134-142 would be allowable if written in independent form. Accordingly, Applicants herein amend claims 134-142 to provide the suggested independent claims. Applicants respectfully submit that the amendments add no new matter and do not alter the scope of the claims, and are merely offered for the benefit of the Examiner and to place the case in better condition for allowance or appeal. Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer or not yet claimed in one or more applications that may claim priority hereto. Applicants respectfully request reconsideration of the rejected claims in view of the following remarks.

35 U.S.C. § 112, First Paragraph, Enablement Rejection

Upon entry of the instant amendments, the only issue remaining in the instant case is a rejection of claims 85-96, 102-106, and 114-133 for lacking enablement. Applicants respectfully traverse this rejection. Applicants disagree that the specification, which the Examiner acknowledges is enabling for assays to determine free and complexed cardiac specific isoforms of troponin using a cocktail of antibodies to provide the necessary binding specificity, is not enabling with regard to assays to determine free and complexed cardiac specific isoforms of troponin using a single antibody that binds to each of the recited troponin forms.

The standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In responding to the previous office action, Applicants noted that the enablement rejection was based entirely upon the unsupported opinion of the Examiner. As such, the Examiner has not established any reasonable basis for questioning the enablement of the claims. *See*, MPEP § 2164.04 (the examiner has the initial burden of establishing a reasonable basis to question enablement; it is incumbent on the Patent Office to explain why it doubts any statement in a disclosure, and to back up its assertions with acceptable evidence or reasoning).

Furthermore, the examiner has improperly dismissed additional evidence supporting enablement provided in the form of a declaration of one of skill in the art, Dr. Kenneth F. Buechler. In the declaration, Dr. Buechler provided a reasoned scientific explanation as to why the skilled artisan, using only routine methods that are well known in the art, could practice the instantly claimed invention without undue experimentation.

Applicants respectfully submit that, by improperly dismissing Applicants' evidence, the Examiner has failed to consider the evidence as a whole, a consideration that is required in any determination of enablement. As stated in MPEP § 2164.05, a declaration or affidavit is, itself, evidence that must be considered. Furthermore, the evidence need not be conclusive, but merely convincing to the skilled artisan. *Id.* In contrast, the Examiner applies an improper standard for proof of enablement, requiring that Applicant must provide conclusive evidence in the form of data that the antibodies of the claims have been generated. *See, e.g.*, Paper No. 15, page 10,

second full paragraph ("Applicant fails to provide evidentiary showing such as in the form of data, that supports generation, selection, and use [of the antibodies referred to in the claims]")..

The declaration of Dr. Buechler is supported by sound scientific reasoning which has not been challenged by the examiner. In contrast, the Examiner's comments concerning lack of enablement of the invention are based solely on personal opinion. As stated in MPEP § 2164.05, the Examiner must never make a determination concerning enablement based on the Examiner's personal opinion (emphasis in original). Applicants respectfully submit that the following analysis of the factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1998) demonstrates that the present claims meet the enablement standard of 35 U.S.C. § 112.

Nature of the Invention

The present invention is directed to assays for cardiac-specific isoforms of troponin. As described in detail in the instant specification, troponin is a muscle protein that regulates contraction. It has three subunits (troponin I, T, and C) that exist in muscle as a ternary troponin T/I/C complex, and there are cardiac-specific isoforms of troponin I and troponin T, allowing troponin from cardiac muscle (as opposed to skeletal muscle) to be specifically identified. *See, e.g.*, specification, page 3, line 29, through page 4, line 7. In blood-derived samples, however, troponin does not necessarily remain as a ternary complex, but instead may circulate as free cardiac-specific troponin I or T, as binary complexes (*i.e.*, two or the three subunits) and/or as the ternary complex (*i.e.*, all three subunits).

The claims are directed to assay methods performed using an antibody that specifically binds each of the three forms of a cardiac-specific troponin isoform: free cardiac-specific troponin isoform, the cardiac-specific troponin isoform in a binary complex, and the cardiac-specific troponin isoform in a ternary complex. This antibody may be a single antibody (*e.g.*, a single monoclonal or polyclonal antibody) or a pool of several antibodies. *See, e.g.*, specification, page 24, lines 21-26.

The Examiner continues to maintain that "the invention is directed to a cocktail of antibodies having specific binding for each and all of free, binary complex, and ternary complex isoforms of [cardiac troponin] (Paper No. 25, page 3, emphasis added), despite the fact that the specification as filed states explicitly that the use of a cocktail of antibodies for this purpose is but one embodiment of the instant invention. For example, the specification explicitly states:

> "[t]he immunoassay may be formulated with a cocktail of antibodies to bind all the troponin complexes and the free troponin I and T. Alternatively, the immunoassay can be formulated with specific antibodies that recognize epitopes of the troponin I and T in the complexes and also the unbound troponin I and T. A preferred immunoassay for troponin I or T involves conjugation of an antibody or a cocktail of antibodies to a label or signal generator to form an antibody conjugate(s), which are capable of binding to cardiac specific regions of the troponin complexes of troponin I or T and to unbound troponin I or T.

Page 24, lines 21-26. This section and others in the specification clearly indicate that the invention is not limited to "cocktails" of antibodies, as the Examiner contends, but rather to methods in which one or more antibodies that bind to each form of a cardiac-specific troponin isoform selected from the group consisting of free cardiac-specific troponin isoform, the cardiac-specific troponin isoform in binary complexes, and the cardiac-specific troponin isoform in ternary complexes are used. Applicants respectfully submit that proper consideration of the nature of the invention is basic to the enablement analysis, and that the Examiner's failure to properly consider the nature of the invention renders the enablement rejection fatally flawed.

State of the Prior Art

Both Applicants and the Examiner acknowledge that the prior art fails to disclose the instantly claimed methods. However, methods for producing antibodies to an antigen of interest are well established in the art.

Level of one of Ordinary Skill

Both Applicants and the Examiner acknowledge that the level of skill in the art of antibody preparation is high.

Predictability in the Art

As discussed above, Applicants have provided a declaration of one skilled in the art, Dr. Kenneth F. Buechler, providing a reasoned scientific basis as to why the skilled artisan would reasonably believe that it would be predictable that antibodies could be obtained that specifically bind each of a free cardiac-specific troponin isoform, the cardiac-specific troponin isoform in a binary complex, and the cardiac-specific troponin isoform in a ternary complex. As discussed in the declaration, a cardiac specific troponin isoform contains various antigenic sites. Because certain antigenic sites may remain available for antibody binding regardless of the complex state of the troponin isoform, these sites may be used to bind the free troponin isoform as well as the troponin isoform in binary and ternary complexes. Nothing of record, other than the Examiner's personal opinion, contradicts this reasoned scientific conclusion.

Moreover, the examples described in the instant invention confirm the accuracy of the scientific basis for Dr. Buechler's statements. For example, Example 23, beginning on page 87 of the specification, describes the selection of antibodies that bind to both free troponin I and to troponin I in a ternary complex with troponin C and troponin T. Similarly, in Example 17 on page 76, the specification describes an assay able to measure both free and ternary complexes of troponin T. As noted on page 76, lines 7-9 and 27-29, the biotinylated anti troponin T peptide 3 antibody is used to formulate such an assay.

According to Dr. Buechler, the skilled artisan would reasonably conclude that such antibodies, which bind to a free troponin isoform and to troponin I/C/T ternary complex, would also bind to the troponin isoform in binary complexes because the site on the troponin isoform to which the antibody binds was not blocked by the presence of the binary complex partner that is necessarily present in the ternary complex. *See, e.g.*, drawing on page 3, of Buechler declaration. Applicants respectfully note that evidence of enablement need not be conclusive, but merely convincing to the skilled artisan. MPEP § 2164.05. Polyclonal antibodies that bind to each of free troponin isoform, the troponin isoform in a binary complex, and the troponin isoform in a ternary complex would be similarly enabled through immunization of an animal with each of

these troponin forms as described in the specification, *e.g.*, on page 21, lines 3-32, and isolating the antibodies produced. Methods for generating polyclonal antibodies have long been well known in the art. *See, e.g., id.*

In contrast to the evidence of predictability in the art provided by Applicant's specification and the declaration of Dr. Buechler, the Examiner offers only the conclusory statement that "there is no predictability" in the art. *See, e.g.*, Paper No. 25, page 3, last paragraph. Such a conclusory statement does not establish a reasonable basis for questioning the enablement provided in the specification. *See*, MPEP § 2164.04 (the examiner has the initial burden of establishing a reasonable basis to question enablement; it is incumbent on the Patent Office to explain why it doubts any statement in a disclosure, and to back up its assertions with acceptable evidence or reasoning).

The Examiner appears to disagree with the conclusion by Dr. Buechler that the skilled artisan would reasonably believe that the antibodies described in the specification would be expected to bind to each of a free troponin isoform, the troponin isoform in binary complexes, and the troponin isoform in ternary complexes, but provides no evidence for questioning the accuracy of Dr. Buechler's declaration. Instead, the Examiner improperly dismisses the scientific explanation provided by Dr. Buechler based on an incorrect standard for proof of enablement, that the specification must provide conclusive evidence that the antibodies which the Examiner considers to be required by the claims have been generated.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would reasonably believe that the antibodies of the instant claims could be obtained using only routine experimentation.

The Amount of Direction or Guidance Present

The instant specification provides extensive guidance as to how antigens should be prepared, and how antibodies should be screened, in order to obtain antibodies that specifically

bind each cardiac-specific troponin form selected from the group consisting of a free cardiac-specific troponin isoform, the cardiac-specific troponin isoform in binary complexes, and the cardiac-specific troponin isoform in ternary complexes. *See, e.g.*, specification, page 21, line 3, through page 24, line 3; Example 22 beginning on page 82; and Example 23, beginning on page 87.

In contrast, the Examiner offers only the conclusory statement that "the specification does not provide any teaching that suggests that an antibody generated against purified free [cardiac troponin isoform], an antibody generated against purified binary complexed [cardiac troponin isoform], or an antibody generated against purified ternary complexed [cardiac troponin isoform] can be characterized to bind a conserved epitope for each and all of [free, binary complexed and ternary complexed troponin isoform]." *See, e.g.*, Paper No. 25, page 6. Again, such a conclusory statement does not establish a reasonable basis for questioning the enablement provided in the specification, which clearly teaches that such antibodies may be produced (*see, e.g.*, page 24, lines 21-26), particularly in view of Dr. Buechler's declaration. As stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." The Examiner has not met this burden.

Furthermore, the Examiner's reply to Applicants' arguments that "nowhere in the specification specifically shows... any generation and selection [of such antibodies]" (Paper No. 25, page 10, first paragraph) again applies an incorrect standard for proof of enablement, that the specification provide conclusive evidence that the antibodies which the Examiner considers to be required by the claims have been generated. The question is not whether such antibodies have been generated, as the Examiner suggests; rather, the question is whether the specification enables such antibodies to be generated without undue experimentation, so that the instant claims may be practiced. Furthermore, as discussed in the following section of this submission, the Examiner is incorrect that no such antibodies are demonstrated in the specification.

Considering the objective evidence of record in its entirety, Applicants respectfully submit that the skilled artisan would acknowledge the extensive guidance provided by the instant specification.

Presence of Working Examples

As discussed by Applicants previously, the examples describe antibodies and assays that measure both free and ternary complexes of cardiac-specific troponin I and T. Because these antibodies rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal, the skilled artisan would acknowledge that both the biotinylated and labeled antibodies must bind to both free and ternary troponin complexes. Further, because the site on the cardiac-specific troponin isoform to which the antibody binds was not blocked in the ternary complex, the skilled artisan would reasonably believe that such antibodies would also be expected to bind to binary troponin complexes.

Despite the fact that this reasoning is based on evidence of record and sound scientific principles, the Examiner's reply indicates that the Examiner disagrees with this reasoning. However the Examiner provides no evidence or reasoning that is inconsistent with this evidence. Instead, the Examiner again simply asserts that nowhere in the examples is such an antibody "specifically" provided. Paper No. 25, page 11, first paragraph.

Considering the objective evidence of record in its entirety, the skilled artisan would acknowledge that working example of the claimed methods are provided by the instant specification.

Quantity of Experimentation Necessary

As described in detain herein, in the Buechler declaration, and in Applicants' prior response, the instant specification describes in detail the claimed assay methods, which use an antibody that specifically binds each cardiac-specific troponin form selected from the group consisting of a free cardiac-specific troponin isoform, the cardiac-specific troponin isoform in

binary complexes, and the cardiac-specific troponin isoform in ternary complexes. The Examiner does not disagree that methods for producing antibodies generally have long been well known and considered routine by those of skill in the art. In view of these facts, Applicants respectfully submit that the quantity of experimentation necessary is not undue.

In contrast, the totality of the Examiner's analysis of this point is to assert without support a conclusion that "it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed." Paper No. 25, page 4, third full paragraph. Again, such an assertion, unsupported by any evidence or reasoning of record, cannot establish a lack of enablement. Moreover, in response to Applicants' arguments in this regard, the Examiner again relies on an assertion that nowhere in the examples is such an antibody actually provided. Paper No. 25, page 11, second full paragraph. Again, evidence of enablement need not be conclusive, but merely convincing to the skilled artisan. MPEP § 2164.05. Finally, as discussed in the previous section of this submission, the Examiner is incorrect that no such antibodies are demonstrated in the specification.

The Instant Claims Meet the Enablement Standard of 35 U.S.C. § 112, First Paragraph

In view of the objective evidence of record, and the foregoing analysis of the factors set forth in *In re Wands*, Applicants respectfully submit that that the present claims meet the enablement standard of 35 U.S.C. § 112, and request that the rejection be reconsidered and withdrawn.

Examiner's Remarks Concerning the Meaning of the Phrase "an antibody"

On page 11, section E, the Examiner appears to take issue with a statement in the declaration of Dr. Kenneth F. Buechler, which stated that the phrase "an antibody" does not refer to a single molecule of antibody, but rather is understood in the art to refer to a single population of antibody. The Examiner asserts in reply that "an antibody" denotes "a singular form of an element." As discussed above, a declaration or affidavit is, itself, evidence that must be

considered. In contrast, the Examiner has cited no evidence for the Examiner's interpretation of the phrase. Applicants also note that the term "antibody" is commonly used in the art to refer to a plural form of an element. For example, a polyclonal antibody, which is a mixture of individual antibody molecules having a variety of specificities, is not "a singular form of an element." Likewise, the phrase "monoclonal antibody" is used to refer to a plural form of a single molecular element. Applicants respectfully request that the Examiner cite some objective evidence in support of the Examiner's interpretation of the phrase "an antibody," or withdraw the remarks.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

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By Barry Wilson

FOLEY & LARDNER
Customer Number: 30542
30542
PATENT TRADEMARK OFFICE
Telephone: (858) 847-6722
Facsimile: (858) 792-6773

Barry S. Wilson
Registration No. 39,431
For
Richard J. Warburg,
Registration No. 32,327
Attorney for Applicant